

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference A2039-7009WO	FOR FURTHER ACTION		See item 4 below
International application No. PCT/JS2006/049278	International filing date (<i>day/month/year</i>) 22 December 2006 (22.12.2006)	Priority date (<i>day/month/year</i>) 23 December 2005 (23.12.2005)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant ALTUS PHARMACEUTICALS INC.			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis 1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | |
|---|---|
| <input checked="" type="checkbox"/> Box No. I | Basic of the report |
| <input type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93da.1 but not, except where the applicant makes an express request under Article 29(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 29, Switzerland Telephone No. +41 22 338 92 79	Date of issuance of this report 24 June 2008 (24.06.2008)
	Authorized officer Nora Lindner e-mail: pu1.psa@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

237

To: James F Halsey Jr
Fish & Neave IP Group
Ropes & Gray LLP
1251 Avenue of the Americas
New York NY 10020

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **05 SEP 2007**

Applicant's or agent's file reference

3862-043-WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 06/49278

International filing date (day/month/year)

22 December 2006 (22.12.2006)

Priority date (day/month/year)

23 December 2005 (23.12.2005)

International Patent Classification (IPC) or both national classification and IPC

IPC(B) - A61K 31/728; A61K 38/00 (2007.01)

USPC - 514/54; 514/12

Applicant
Aitua Pharmaceuticals Inc

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 56.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Communications for Patents
P.O. Box 1480, Alexandria, Virginia 22313-1480
Facsimile No. 571-273-3261

Date of completion of this opinion

09 July 2007 (09.07.2007)

Authorized officer

Lee W. Young

PCT Helpdesk: 571-477-4226
PCT OIR: 571-273-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/49278

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43b(4)(a)).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/49278

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-19 and 21-22

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 16-19 and 21-22 are so unclear that no meaningful opinion could be formed (specify):

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6A(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (specify):

☒ no international search report has been established for said claims Nos. 16-19 and 21-22

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-6a of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing. If in electronic form only, do not comply with the technical requirements provided for in Annex C-6a of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 08/49278

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15, 20, 23-32	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-15, 20, 23-32	NO
Industrial applicability (IA)	Claims	1-15, 20, 23-32	YES
	Claims	None	NO

2. Citations and explanations

Claims 1-15, 20 and 23-32 lack an inventive step as defined by PCT Article 33(3) as being obvious over US 2004/0209804 A1 to Govardhan et al. (hereinafter "Govardhan") in view of US 2003/0176288 A1 to Margolin et al. (hereinafter "Margolin").

As to claims 1-3, Govardhan teaches a composition comprising a polycation-complexed protein crystal (claim 1) (para [0058], divalent crystals of hGH). Govardhan also teaches a composition comprising a polycation-complexed protein crystal, wherein said crystal is a cation crystal (claim 2) and wherein said crystal is a monovalent cation crystal (claim 3) (para [0068], the monovalent cation salt is a sodium salt). Govardhan does not teach complexed protein crystals and hyaluronic acid. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]). It would have been obvious to one of ordinary skill in the art to combine the teachings of Govardhan and Margolin because both of them teach human growth hormone protein crystals and methods of preparing them for human therapeutic treatments.

As to claims 4-6, directed to the composition of claims 1-3, 4 and 3, respectively, wherein the protein is a growth hormone (claim 4); wherein said growth hormone is human growth hormone (claim 5); and, wherein the monovalent cation is sodium (claim 6), are further obvious because Govardhan teaches "monovalent [...] crystals of hGH [...] the crystals are sodium crystals" (para [0058]). Govardhan does not teach complexed protein crystals and hyaluronic acid. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]).

As to claims 7-8, directed to the composition of claims 1-3 and 7, respectively, wherein the polycation is selected from the group consisting of polyarginine (claim 7) and wherein said polycation is polyarginine (claim 8), are further obvious because Govardhan teaches "the crystals are [...] complexed or co-crystallized with [...] polyarginine" (para [0058]).

As to claims 9-10, directed to the composition of claims 1-3, Govardhan further teaches "the excipient is selected from the group consisting of: amino acids, salts [...] polyanionic acids and mixtures thereof" (para [0055]) and "this invention advantageously permits sustained release of hGH into a mammal" (para [0083]).

As to claims 11-12, directed to the composition of claims 1-3, Govardhan further teaches "the crystals or compositions [...] are administered by subcutaneous route using a needle having a gauge greater than or equal to 27 [...] the needle gauge may be equal to 30" (para [0082]).

As to claims 13-14, Govardhan further teaches a method for treating a mammal in need of protein therapy (claim 13); and, a method for treating a mammal having a disorder associated with hGH deficiency (claim 14) comprising administering to said mammal a therapeutically effective amount of a composition according to claims 1-3 and 4, respectively, claim 23, a method for treating a mammal having a disorder associated with human growth hormone deficiency or which is ameliorated by treatment with human growth hormone comprising the step of administering to said mammal a therapeutically effective amount of a crystal [...] or composition).

As to claim 15, directed to the method of claim 14, is further obvious because Govardhan teaches "the method [...] wherein said disorder is selected from the group consisting of: adult growth hormone deficiency [...] Crohn's disease and burns" (claim 26).

As to claim 20, Govardhan further teaches a method for improving injection site tolerance in a mammal comprising the step of administering to said mammal a composition according to any one of claims 1-3 (para [0062], the crystals or compositions may be administered [...] by needle-free injection).

As to claim 23, Govardhan further teaches a polycation complexed crystal (para [0058], monovalent or divalent crystals of hGH [...] complexed or co-crystallized with [...] polyarginine). Govardhan does not teach the step of adding hyaluronic acid to said polycation-complexed crystal. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]). It would have been obvious to one of ordinary skill in the art to combine the teachings of Govardhan and Margolin because both of them teach human growth hormone protein crystals and methods of preparing them for human therapeutic treatments.

—continued in Supplemental Box—

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From the
INTERNATIONAL SEARCHING AUTHORITY

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To: James F Halsey Jr
Fish & Neave IP Group
Ropes & Gray LLP
1251 Avenue of the Americas
New York NY 10020

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **05 SEP 2007**

Applicant's or agent's file reference

3862-043-WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 06/48278

International filing date (day/month/year)

22 December 2006 (22.12.2006)

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23 December 2005 (23.12.2005)

International Patent Classification (IPC) or both national classification and IPC

IPC(B) - A61K 31/728; A61K 38/00 (2007.01)

USPC - 514/54; 514/12

Applicant

Altus Pharmaceuticals Inc

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- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
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Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Comptroller for Patents
P.O. Box 1480, Alexandria, Virginia 22313-1480
Facsimile No. 571-273-3261

Date of completion of this opinion

09 July 2007 (09.07.2007)

Authorized officer

Lee W. Young

PCT Helpdesk: 571-477-4226
PCT OIR: 571-273-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/49278

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 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
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 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
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 - ☐ contained in the international application as filed
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5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/49278

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-19 and 21-22

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 16-19 and 21-22 are so unclear that no meaningful opinion could be formed (specify):

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6A(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (specify):

☒ no international search report has been established for said claims Nos. 16-19 and 21-22

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/49278

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-15, 20, 23-32	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-15, 20, 23-32	NO
Industrial applicability (IA)	Claims	1-15, 20, 23-32	YES
	Claims	None	NO
2. Citations and explanations:			
<p>Claims 1-15, 20 and 23-32 lack an inventive step as defined by PCT Article 33(3) as being obvious over US 2004/0209804 A1 to Govardhan et al. (hereinafter "Govardhan") in view of US 2003/0176288 A1 to Margolin et al. (hereinafter "Margolin").</p> <p>As to claims 1-3, Govardhan teaches a composition comprising a polycation-complexed protein crystal (claim 1) (para [0058], divalent crystals of hGH). Govardhan also teaches a composition comprising a polycation-complexed protein crystal, wherein said crystal is a cation crystal (claim 2) and wherein said crystal is a monovalent cation crystal (claim 3) (para [0068], the monovalent cation salt is a sodium salt). Govardhan does not teach complexed protein crystals and hyaluronic acid. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]). It would have been obvious to one of ordinary skill in the art to combine the teachings of Govardhan and Margolin because both of them teach human growth hormone protein crystals and methods of preparing them for human therapeutic treatments.</p> <p>As to claims 4-6, directed to the composition of claims 1-3, 4 and 3, respectively, wherein the protein is a growth hormone (claim 4); wherein said growth hormone is human growth hormone (claim 5); and, wherein the monovalent cation is sodium (claim 6), are further obvious because Govardhan teaches "monovalent [...] crystals of hGH [...] the crystals are sodium crystals" (para [0058]). Govardhan does not teach complexed protein crystals and hyaluronic acid. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]).</p> <p>As to claims 7-8, directed to the composition of claims 1-3 and 7, respectively, wherein the polycation is selected from the group consisting of polyarginine (claim 7) and wherein said polycation is polyarginine (claim 8), are further obvious because Govardhan teaches "the crystals are [...] complexed or co-crystallized with [...] polyarginine" (para [0058]).</p> <p>As to claims 9-10, directed to the composition of claims 1-3, Govardhan further teaches "the excipient is selected from the group consisting of: amino acids, salts [...] polyanionic acids and mixtures thereof" (para [0055]) and "this invention advantageously permits sustained release of hGH into a mammal" (para [0083]).</p> <p>As to claims 11-12, directed to the composition of claims 1-3, Govardhan further teaches "the crystals or compositions [...] are administered by subcutaneous route using a needle having a gauge greater than or equal to 27 [...] the needle gauge may be equal to 30" (para [0082]).</p> <p>As to claims 13-14, Govardhan further teaches a method for treating a mammal in need of protein therapy (claim 13); and, a method for treating a mammal having a disorder associated with hGH deficiency (claim 14) comprising administering to said mammal a therapeutically effective amount of a composition according to claims 1-3 and 4, respectively, claim 23, a method for treating a mammal having a disorder associated with human growth hormone deficiency or which is ameliorated by treatment with human growth hormone comprising the step of administering to said mammal a therapeutically effective amount of a crystal [...] or composition).</p> <p>As to claim 15, directed to the method of claim 14, is further obvious because Govardhan teaches "the method [...] wherein said disorder is selected from the group consisting of: adult growth hormone deficiency [...] Cushing's disease and burns" (claim 26).</p> <p>As to claim 20, Govardhan further teaches a method for improving injection site tolerance in a mammal comprising the step of administering to said mammal a composition according to any one of claims 1-3 (para [0062], the crystals or compositions may be administered [...] by needle-free injection).</p> <p>As to claim 23, Govardhan further teaches a polycation complexed crystal (para [0058], monovalent or divalent crystals of hGH [...] complexed or co-crystallized with [...] polyarginine). Govardhan does not teach the step of adding hyaluronic acid to said polycation-complexed crystal. Margolin further teaches: "polymers used for encapsulation of protein crystals for delivery of proteins, including biological delivery [...] the polymeric carrier may be [...] hyaluronic acid" (para [0174]). It would have been obvious to one of ordinary skill in the art to combine the teachings of Govardhan and Margolin because both of them teach human growth hormone protein crystals and methods of preparing them for human therapeutic treatments.</p>			
-----continued in Supplemental Box-----			